MAITAKE EXTRACT FOR BREAST CANCER: PRELIMINARY RESEARCH AND SUBSEQUENT CLINICAL TRIALS

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Introduction: Maitake extract, a botanical product widely used with chemotherapy to treat breast cancer in Asia, is prepared from the Japanese maitake mushroom, a traditional Asian herbal medicine. It has potent immunostimulant effects: Maitake potentiates the cytotoxicity of natural killer cells, activates macrophages, enhances antibody responses and induces tumor necrosis factor-α and interleukin-1β. In mouse studies, maitake reduces the weight of primary breast tumors and the number of metastatic sites. The objective of this grant is to conduct laboratory studies of maitake prior to human clinical trials. Initial goals are to generate additional laboratory data to standardize the maitake preparation, confirm immune activity, test interactions between maitake and conventional chemotherapy, and evaluate maitake's effects on the formation and development of stem cells.

Methods: To test immune activity, human monocyte cell line U937 and mouse macrophage cell line RAW264.7 were treated with maitake extract and consequent release of tumor necrosis factor-α and interleukin-1β evaluated. *In vitro* cytotoxicity studies combined various concentrations of maitake with Taxol or Taxotere with MCF7 breast cancer cells. Mouse bone marrow cells were exposed to different concentrations of maitake with or without concurrent or pretreatment with doxorubicin, and the effect on stem cell growth was evaluated by colony forming unit-granulocyte/macrophage (CFU-GM) assay. Standardization data are forthcoming.

Results: Maitake extract demonstrated biological activity, increasing production and release of tumor necrosis factor-α at 8 hours and through 72 hours on both cell lines. Spontaneous release of interleukin-1β occurred with increased doses of maitake. In vitro, maitake did not interfere with the cytotoxicity of Taxol or Taxotere. Exposure of mouse bone marrow cells to maitake alone increased CFU-GM. Maitake protected CFU-GM against doxorubicin toxicity and recovered CFU-GM from doxorubicin-pretreated bone marrow cells.

Clinical study plans: In a Phase I trial, healthy volunteers will be given oral maitake and blood samples taken to measure oral bioavailability and immune response. These results will be used to determine the dosage of maitake extract to be used in clinical trials with breast cancer patients.

Conclusions: Maitake extract appears to exert activity not via direct action against tumor cells, but indirectly through enhancement of immune function. There are important potential clinical implications, which we will test in patient trials. Eventually, women with breast cancer could receive an agent with minimal toxicity (maitake extract) that may (1) increase the benefits of chemotherapy; (2) decrease chemotherapy toxicity; (3) decrease bone marrow suppression, and (4) enhance tumor cell kill through immune system enhancement.

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ANTICIPATED AND UNANTICIPATED ESTROGENICITY OF SEVERAL MEDICINAL BOTANICALS

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Medicinal botanicals are used by traditional herbal medicine practitioners for gynecological complaints, as tonics, and for depression and other chronic illnesses. Such botanicals are of increasing interest to those seeking alternative health care and self-treatment. However, women who have or are at risk for breast cancer pose a particular problem when using such materials, since little is known about their safety, potency, and hormonal properties. Our previous work has identified several plant extracts from Western and Chinese cultures that are traditionally used for gynecological complaints and which demonstrate estrogenic activity in vivo and in vitro. Extracts of dang gui root, black and blue cohosh roots, vitex berry, hops flower, wild yam root and licorice root were shown to interact with the estrogen receptor in vitro, and to induce estrogenic responses in ovariectomized female rats and in cell lines. In the current study, additional extracts were tested for estrogenic potency in an in vitro competitive estrogen receptor (ER) binding assay performed in parallel with diethylstilbestrol. Significant dose-dependent inhibition of radiolabelled estradiol binding to ER was observed with several extracts. Most potent are, in descending order, Rhodiola rosea root, saw palmetto berry, elecampane root, red clover blossom, dang gui root, astragalus root, and alfalfa leaf. Extracts of motherwort leaf, yarrow flower, and asparagus root exhibited moderate competition, while extracts of maca root, turmeric root, and cramp bark, exhibited slight competition in this assay. While several of these extracts are traditionally used for gynecological complaints (dang gui, motherwort, cramp bark, red clover), Rhodiola rosea, maca, and astragalus are used as adaptogens and tonics, and saw palmetto is used by men as a treatment for benign prostatic hyperplasia. These results indicate that some herbal remedies demonstrate measurable estrogenic activity, in spite of the fact that they are not traditionally used as such. The estrogenic medicinal botanicals may have clinical applications; conversely, these herbs might be avoided in conditions in which estrogens are contraindicated.

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HOMEOPATHY FOR HOT FLASHES IN BREAST CANCER SURVIVORS

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Hot flashes, and other symptoms of estrogen withdrawal, are common in both pre- and post-menopausal breast cancer survivors. The standard treatment for these symptoms, hormone replacement therapy, is contraindicated in breast cancer survivors. Homeopathic medicines have been used to treat hot flashes and other menopausal symptoms for more than 100 years. Our goal was to determine whether homeopathy is an effective treatment to improve the quality of life in breast cancer survivors who are experiencing hot flashes and other menopausal-type symptoms.

We carried out a pilot study to demonstrates our ability to successfully conduct a full-scale trial. A group of 83 breast cancer survivors with hot flashes and other menopausal symptoms were randomized to one of three treatment arms: classical homeopathy, a combination homeopathic remedy, or placebo. The number of hot flashes, menopausal index scores, general health status, patient satisfaction, and the use of health care services were measured over a period of 12 months.

Recruitment was slower and more difficult than anticipated. We expanded recruitment to another medical center and extended the recruitment period for an additional seven months, to obtain a total of 83 patients in the study, 79% of our projected goal of 105. Withdrawals were higher than anticipated, with a total of 28 withdrawals from the study (33.7% of the total cohort). Of these, 12 (44%), reported no relief from hot flashes, 7 (25%) had a cancer recurrence or were advised to withdraw by their physicians, 5 (18.5%) said the study was too inconvenient, and 4 (15%) were lost to follow-up. However, 66 of the 83 originally enrolled completed at least six months of the study (80%). We plan to look at the withdrawal rate by study arm to see whether those receiving placebo had a higher withdrawal rate.

In future studies, recruitment should be more aggressive, with a larger budget for advertisements in the local media and gift incentives for subjects. We also recommend that the study period be shortened to six months, as it is unreasonable to expect women who are not receiving relief from hot flashes to continue for one year. The public health importance of a natural treatment for hot flashes in breast cancer survivors would be great.

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SELF-HYPNOTIC RELAXATION AS AN ADJUNCT TO LOCAL ANAESTHESIA DURING LARGE-CORE BREAST BIOPSY

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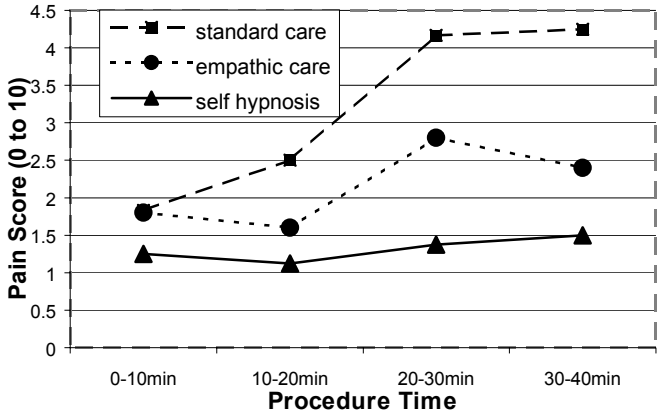
Large core breast biopsy is well established for diagnosis of breast cancer but can tax the coping mechanisms of even well functioning individuals. This study assesses whether self hypnotic relaxation during the breast biopsy reduces intra- and postoperative distress.

The plan is to randomize 240 patients to receive during their large core breast biopsies (a) standardized self-hypnotic relaxation, (b) structured empathic attention, or (c) standard care. Patients rate pain and anxiety on 0-10 self-rating scales before, during, and after their procedures. Six weeks into the active enrollment phase, of 19 patients, six were randomized to standard care, five to empathic attention, and eight to self hypnosis.



Results: Pain increased with procedure time in the standard group (as had been shown previously with patients undergoing invasive vascular procedures; Lang et al, Lancet 2000; 29:355). The increase in pain was less in the empathy group. Pain did not increase with self-hypnotic relaxation. After the procedure, patients in the hypnosis group experienced less pain (mean score 0.8) than those in the empathy and standard groups (mean scores 2.2 and 2.5), and also had less anxiety (mean score 0.25 vs 4.2 and 3.8). Hypnosis did not prolong procedure time.

This research is important since it provides a simple, time-sensitive biobehavioral intervention which decreases patient distress and promises to have longer-lasting effects on psycho-physiologic phenomena.

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A CONTROLLED STUDY USING ACUPUNCTURE AS AN ADJUVANT TO TREAT CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

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Nausea and vomiting (N/V) are significant side effects of cancer chemotherapy which can both affect a patient's quality of life and compromise a physician's ability to deliver adequate doses of effective chemotherapy. This is a randomized, double blind controlled study designed to assess the effects of electroacupuncture (EA) on N/V induced by chemotherapy in cancer patients. The primary aim of this study is to evaluate the usefulness of EA as an adjuvant on N/V in chemotherapy patients who do not respond to conventional antiemetics.

Seventy-five outpatients are recruited from the University of Maryland Baltimore (UMB) Cancer Center who have shown refractory to 5-HT3 antiemetic and randomized into three treatment groups (n=25 per group): (1) EA: 10 Hz, 20 min, (2) EA: 100 Hz, 20 min, and (3) a sham acupuncture control group.

101 patients had been screened, 18 judged as eligible, and 10 have consented to go on the protocol and have now completed the study. Complete data have been obtained from the 10 participating patients and the procedures appear to be working quite well, although no analyses have been performed to date. No subjects have withdrawn and no serious adverse events due to acupuncture treatment have been observed. However, the study has experienced difficulty with obtaining sufficient numbers of patients due to the low prevalence of N/V among the chemotherapy patients at the UMB Cancer Center. For this reason an amendment has been approved by the UMM IRB and submitted for approval to the DOD to 1) extend the study to include the Cancer Center's Bone Transplant Unit (BTU) inpatients who receive more aggressive chemotherapy, and 2) to drop one of the treatment group to include only 10 Hz EA treatment group so sample size will be reduced to 50 total.

In conclusion, this is an on-going study to investigate the effect of EA on N/V induced by chemotherapy in the cancer patients. However, we have been experiencing unexpected slow enrollment. It is hoped that by expanding the pool of participants in BTU and modified sample size, the study will have a sufficient number of participants to complete the project.

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PHASE I PILOT STUDY TO ASSESS TOXICITY AND EFFICACY OF CHINESE HERBS TO TREAT HOT FLASHES AND MENOPAUSAL SYMPTOMS

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Menopausal symptoms are common in women with breast cancer due to natural or treatment-induced menopause. Since estrogen therapy is generally avoided in this population, herbal regimens are commonly used despite lack of information regarding effectiveness and safety. The purpose of this study is to assess the safety and feasibility of a Chinese herbal formula (MF101) when used to alleviate hot flashes and other symptoms associated with menopause. Additionally, indices of estrogenic activity in vaginal epithelium, serum measures of bone resorption, and serum and urinary estrogen and estrogen metabolites will be assessed prior to and following a regimen of MF101. The study involves a 30-day run-in period followed by a 30-day treatment period during which patients without a history of breast cancer receive MF101 daily. Patients are asked to record hot flashes during the entire 60-day study period. A total of 20 patients will be recruited for the study and, thus far, 3 patients have completed the study and 5 patients are currently in the treatment portion of the study. No Grade I-IV toxicities have been reported thus far due to MF101. For the three currently evaluable patients, the total number of hot flashes for the run-in period and the treatment period are 7.75 + 2.14 (mean + SD) and 4.53 + 2.55, respectively. The prescribed dosage for MF101 is 5 grams of granulated powder mixed with warm water twice per day, and patients have reported compliance of 1.88 + 0.33 doses per day. After demonstration of safety and an estimation of reduction of hot flashes, a placebo-controlled double-blind randomized cross-over study in women with a history of breast cancer is planned.

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